Pending claims

Claims 1-64 are pending. Upon entry of this amendment, claims 1-64 are canceled without prejudice to pursuing these or related claims in a continuation or other related applications. Claims 65-71 are presented for examination.

Support for newly added claims may be found throughout the specification, and at least at page 10, lines 10-27, page 11, lines 14-15, page 23, line 21, through page 24, line 12, page 25, lines 10-15, page 38, lines 7-10, and page 67, lines 25-27, through page 68, lines 1-2, Example 2, and in the claims as originally filed (see, e.g., originally filed claim 4).

The claimed invention provides a method of screening for the presence of an autoimmune disease associated with a reduction in NFκß activity by detecting a reduction in proteosome activity as determined by measuring the level of NFκß proteolytic products. As discussed in the specification at page 38, lines 4-10, such an assay may be used to facilitate early diagnosis of an autoimmune disease in an individual suspected to be at risk for such a disease.

Rejection of Claims 1 and 4 Under 35 U.S.C. § 112 First Paragraph

Claims 1 and 4 were rejected under 35 U.S.C. § 112 First Paragraph for failing to provide enablement for detecting any autoimmune disease by detecting a reduction in the proteolytic processing of NFκß. The Examiner asserts that the specification discloses only one working example correlating a reduction in the proteolytic processing of NFκß with autoimmune disease and that because the art does not report an association between a reduction of proteolytic processing of NFκß with autoimmune disease, Applicants' invention requires undue experimentation.

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Applicants have canceled claims 1 and 4; however, to the extent that the rejection would be applied to the newly added claims, Applicants respectfully traverse the rejection. As stated in *In re Marzocchi,* 439 F.2d 220, 223, (C.C.P.A. 1971):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless there is reason to doubt* the objective truth of the statements contained therein which must be relied on for enabling support *(emphasis added).*

Applicants' respectfully submit that the specification provides specific guidance and working examples to enable the genus claimed and that the Examiner has not provided any reason to doubt the objective statements made in the specification.

The specification identifies a variety of autoimmune diseases whose effects may be correlated with reduced proteolytic processing of NFκß, including Addison's disease (page 29), ulcerative colitis and Crohn's disease (page 31), lupus erythematosus (page 31), Sjörgen's syndrome (page 32), Type I diabetes (page 33-34), multiple sclerosis (page 35), rheumatoid arthritis (page 36), Hashimoto's disease (page 37), Grave's disease, vitiligo (page 37), psoriasis (pages 37-38), pemphigus vulgaris (page 38), and others. Despite the different clinical manifestations of these diseases, they share many physiological responses in common, such as fatigue, inflammation, paresis, joint stiffness, pain or swelling, skin lesions or nodules, skin discoloration, enzymatic imbalances, and tissue degeneration, which may be used as common diagnostic indicators of the presence of an autoimmune disease (see page 8 of the specification, last paragraph through page 9, bridging paragraph; see, also U.S. Patent No. 5,962,516, column 2, lines 26-28; U.S. Patent No. 5,888,511, column 2, lines 10-13; and U.S. Patent No. 5,506,213, column 3, line 65, through column 5, line 60; provided in Applicants' Supplemental Information

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Disclosure Statement (SIDS) filed herewith). Indeed, the finding of common genetic susceptibility loci involved in the pathogenesis of autoimmune diseases. See, e.g., as discussed in Becker et al., Proc. Natl. Acad. Sci. USA 95(17): 9979-9984, 1998 and Heward et al., Clinical Science 93: 479-491, 1997, provided with Applicants' SIDS further supports the use of assays to identify defects in the products of "master genes" or common loci shared in multiple autoimmune diseases. As discussed in Becker et al, *supra,* at page *7 (of the web-published article), last paragraph, "shared genes among distinct [autoimmune] diseases may lead to common early diagnostic criteria and therapeutic strategies."

It is well known that NFκß plays a central role in regulating physiological responses to autoimmune disease by regulating the expression of cytokines, cell adhesion molecules, and other proteins (see, as discussed in Adams, WO 96/13266, Kopp and Ghosh, Science 265: 956-969, 1994, and Grilli, et al., Science 274: 1384-1385, 1996, cited in the specification at page 7, and Grilli, et al., Int. J. Cytology 143: 1-62, 1993, cited at page 43; each of these references having been provided with Applicants' Information Disclosure Statement (IDS), filed October 6, 1998; see, also U.S. Patent No. 6,117,911, Example VII, provided herewith). Thus, the use of NFκß to identify malfunctions in the common processes implicated in the pathogenesis of autoimmune responses is well supported by both Applicants' specification and the prior art.

The Examiner has acknowledged that the specification is enabling for a method of detecting diabetes by detecting a reduction in the proteolytic processing of NFκß, apparently, because Applicants have exemplified the success of their method using NOD mice (e.g., Example 2). However, NOD mice are not solely animal models for the specific symptoms presented in Type I diabetes mellitus. As discussed in the specification at page 39, lines 3-4, these animals are also widely recognized as models of the clinical manifestations of Sjögren's syndrome and autoimmune hemolytic anemia. Further, as discussed at page 40, lines 24 through

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bridging paragraph on page 41, NOD mice can be considered as models of some of the common processes observed in *all* autoimmune diseases by virtue of the abnormal antigen presentation and processing observed in these mice. Therefore, Applicants' finding that NOD mice lack the proteosome-processed active form of NFκß (see page 88, lines 16-18, of Applicants' specification), in view of all that is known in the prior art about the relationship between NFκß activity and universal autoimmune disease processes, such as inflammation and tissue destruction (see, as discussed in the references cited in the previous paragraph), provides an ample expectation of success for an assay for screening for the presence of an autoimmune disease correlated with decreased NFκß activity as claimed in the present application. The specification also provides ample guidance for performing such an assay by identifying a number of assays that are routine in the art which may be used to measure reduced proteosome activity (see, e.g., pages 23-24 and page 67 of the specification).

In view of the above arguments, Applicants respectfully submit that the Examiner has not met the burden of demonstrating any reasons to doubt the objective truth of the statements contained in Applicants' specification, as required for a rejection under section 112, first paragraph. Accordingly, Applicants respectfully submit that the rejection is improper and should be reconsidered and withdrawn.

Rejection of Claims 1-3 and 5-7 Under 35 U.S.C. § 102(b)

Claims 1-3 and 5-7 were rejected under 35 U.S.C. § 102 (b) as being anticipated under U.S. Patent No. 5,538,854 ("the '854 patent"). The Examiner asserts that the '854 patent teaches the detection of Hashimoto's disease by detecting a defect in a proteosome in a biological sample and comparing the defect to a wild type proteosome to detect an autoimmune disease. The Examiner asserts that, "When the claims are read in the light of the specification, the term

reduction of proteosome activity is interpreted broadly to encompass detecting genetic defects which then leads to irregular processing of proteosome products."

Applicants respectfully traverse this rejection. As amended, the claims recite an assay for screening for the presence of an autoimmune disease associated with *reduced NFκß activity* and requires that proteosome *activity* (i.e., not merely proteosome levels) be measured by determining the level of *NFκß proteolytic products* of proteosomes from a cell sample. In contrast, the '854 patent describes "determining a defect in or a deletion in a gene involved in the processing or transport of endogenous proteins into the endoplasmic reticulum for complexation with HLA class I molecules" (column 2, lines 59-67 through column 3, lines 1-2) as a means of detecting defects in HLA class I molecules (column 6, lines 44-53) and teaches measuring this defect by performing any of "Western blot analysis, mRNA Northern blot analysis, cell surface protein phenotyping, or restriction fragment length polymorphism (RFLP) analysis, single-stranded chain polymorphism, denaturing gel electrophoresis, or polymerase chain-reaction" (see column 3, lines 7-12).

Thus, the '854 patent nowhere teaches measuring the *activity* of a proteosome by detecting altered *NFκß proteolytic products*. Instead, the '854 patent only teaches determining the level of expression of the *proteosome itself or its structure*. Further, the '854 patent does not teach screening for autoimmune disease *associated with a reduction in NFκß activity* in a mammal deemed to be at risk for an autoimmune disease. Therefore, Applicants respectfully submit that because the reference does not teach every element of the amended claims, that the rejection should be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

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